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ENDOGENOUS HISTAMINE AND PROMETHAZINE-INDUCED GASTRIC ULCERS IN THE GUINEA PIG

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Translation of "Histamine endogène et ulcères gastriques prométhaziniques chez le Cobaye," Thérapie, XXV, 1970, pp. 611-614.

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16. Abstract

Experiments performed with an inhibitor of diaminoxydase, aminoguanidine and an inhibitor of histidine decarboxylase, NSD 1055, showed that the frequency of gastric ulcers induced by promethazine was increased with the first inhibitor and decreased with the second. It was suggested that ulcers induced by promethazine in guinea pigs might be due to histamino-liberator effect of the antihistaminio compound.

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ENDOGENOUS HISTAMINE AND PROMETHAZINE-INDUCED GASTRIC ULCERS IN THE GUINEA PIG

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In a preliminary study, we demonstrated the ulcerogenic /611* effect of promethazine hydrochloride on the guinea pig [1]. We also showed that the development of these ulcers, unlike that of stress ulcers[2], is not dependent on the sympathetic nervous system[3].

Schwartz et al[4], studying the role of histamine in the development of experimental gastric ulcers, showed that previous administration of an inhibitor of diaminoxidase, aminoguanidine, or of a specific inhibitor of histadine decarboxylase, bromo-4-hydroxy-3-benzyl-oxyamine (NSD 1055), to rats subjected to various ulcerogenic methods (stress, injection of phenylbutazone or reserpine) does not change the number of ulcers.

Because of the histamine-releasing properties of antihistamines, especially promethazine, we expressed the hypothesis that the production of gastric ulcers by promethazine could be due to the histamine-releasing properties of this drug.

If the production of promethazine-induced gastric ulcers is due to the release of histamine, all drugs capable of decreasing the biogenesis of histamine (NSD 1055), or the deterioration of endogenous histamine (aminoguanidine) should change the ulcerogenic action of promethazine.

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* Numbers in the margin indicate pagination in the foreign text.

Methods

The study dealt with 70 guinea pigs, weighing 350 - 450 g /612 half male and half female. The animals live in an animal house in individual cages with food and water ad libitum. They are given no food or water 24 hours before the experiment. The guinea pigs are divided into two groups: a "control" group of 10 guinea pigs, and an experimental group of 60 guinea pigs. the latter is divided into three sections, 20 animals each (Sections II, III, and IV). The control animals receive 1 ml/100 g of NaCl solute at 8.5 per 1000 by intraperitoneal injection. Promethazine hydrochloride, aminoguanidine, and NSD 1055, placed in solution in the NaCl solute at 8.5 per 1000, are are intraperitoneally injected in quantities of 3 ml per animal and administered according to the following plan:

1) NSD (150 mg/kg) and aminoguanidine (10 mg/kg) are administered to animals of Sections II and III respectively at 0 time.

2) Promethazine hydrochloride (87.5 mg/kg, a dose which produces ulcers in 50% of the animals) is injected into the guinea pigs of Sections II, III and IV at +30 min. At +5 hrs. 30 min. the animals are sacrificed by a blow on the nape of the neck. The stomach is opened along the large curvature, carefully cleaned with water and examined under a microscope. The stomachs having distinct necrohemorrhagic lesions are considered to be ulcerous. The presence of ulcers is confirmed by a histological examination. The statistical analysis of the results is made according to the formula

$$\left[x' = \frac{(f - F)'}{F} \right].$$

Results

The results are summarized in the following table. They show that:

1) The control animals showed no ulcerous lesions.

2) The percentage of ulcers in the animals treated by promethazine was shown to be comparable to that obtained in our laboratory during previous studies [1].

3) The administration of a single dose of NSD 1055 leads to a decrease in the percentage of promethazine-induced ulcers. The adminsstration of aminoguanidine leads to a significant increase in ulcers.

Discussion

Mota and Dias Da Silva [5] have shown that among the /613 antihistamines, promethazine is a powerful histamine releaser. On the other hand, Amuré and Ginsburg [6] revealed that in the rat, the secretory action of gastrin, which seems to be exercised by means of gastric histamine, is potentiated by aminoguanidine.

TABLE - EFFECT OF AMINOGUANIDINE AND NSD 1055 ON PROMETHAZINE HYDROCHLORIDE-INDUCED ULCERS IN THE GUINEA PIG

a) Groupe	b) Produit	Dose mg/kg	d) Nombre des cobayes	e) Nombre des animaux porteurs d'ulcères	f) Pourcentage des cobayes ulcéreux
I	c) Sérum salé isotonique	—	10	—	—
II	NSD 1055 + promethazine	150 87,5	20	3	15 (*)
III	Aminoguanidine + promethazine	10 87,5	20	18	90 (*)
IV	Promethazine	87,5	20	10	50 (**)

The differences between (*) and (**) are significant for $p < 0.005$.

Key: a) Group, b) Product, c) Normal saline solution, d) Number of guinea pigs, e) Number of animals with ulcers, f) Percentage of guinea pigs with ulcers

The statements of these authors led us to assume that ulcers produced by promethazine are due to the release of histamine. This hypothesis seems to be confirmed by the experimental results which we obtained: increase by aminoguanidine (inhibitor of diaminoxidase) of the percentage of animals afflicted with ulcers, and a decrease in this percentage by use of NSD 1055 (inhibitor of histidine decarboxylase).

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